

Claims

What is claimed is:

*Sub B1* ✓ 1. A targeted therapeutic delivery system comprising a gas or gaseous precursor filled microsphere wherein said gas or gaseous precursor filled microsphere comprises an oil, a surfactant, and a therapeutic compound.

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✓ 2. The targeted therapeutic delivery system of claim 1 wherein the microsphere comprises a gaseous precursor selected from the group consisting of fluorine, perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane, perfluoropentane, perfluorohexane, sulfur hexafluoride, hexafluoropropylene, bromochlorofluoromethane, octafluoropropane, 1,1 dichloro, fluoro ethane, hexa fluoroethane, hexafluoro-2-butyne, perfluoropentane, perfluorobutane, octafluoro-2-butene, hexafluorobuta-1,3-diene, octafluorocyclopentene, hexafluoroacetone, isopropyl acetylene, allene, tetrafluoro allene, boron trifluoride, 1,2-butadiene, 1,3-butadiene, 1,2,3-trichloro,2-fluoro-1,3-butadiene, 2-methyl,1,3-butadiene, hexafluoro-1,3-butadiene, butadiene, 1-fluoro-butane, 2-methyl-butane, decafluoro butane, 1-butene, 2-butene, 2-methyl-1-butene, 3-methyl-1-butene, perfluoro-1-butene, perfluoro-2-butene, 4-phenyl-1-butene-2-one, 2-methyl-1-butene-3-yne, butyl nitrate, 1-butyne, 2-butyne, 2-chloro-1,1,1,4,4-hexafluoro-butyne, 3-methyl-1-butyne, perfluoro-2-butyne, 2-bromo-butylaldehyde, carbonyl sulfide, crotononitrile, cyclobutane, methyl-cyclobutane, octafluoro-cyclobutane, perfluoro-cyclobutene, 3-chloro-cyclopentene, cyclopropane, 1,2-dimethyl-cyclopropane, 1,1-dimethyl-cyclopropane, 1,2-dimethyl cyclopropane, ethyl cyclopropane, methyl cyclopropane, diacetylene, 3-ethyl-3-methyl diaziridine, 1,1,1-trifluoro-diazoethane, dimethyl amine, hexafluoro-dimethyl amine, dimethylethylamine, bis-(Dimethyl phosphine)amine, 2,3-dimethyl-2-norbornane, perfluoro-dimethylamine, dimethyloxonium chloride, 1,3-dioxolane-2-one, 4-methyl, 1,1,1,2-tetrafluoro ethane, 1,1,1 trifluoroethane, 1,1,2,2-tetrafluoroethane, 1,1,2-trichloro-1,2,2-trifluoroethane, 1,1 dichloro ethane, 1,1-dichloro-1,2,2,2-tetrafluoro ethane, 1,2-difluoro ethane, 1-chloro-1,1,2,2-pentafluoro ethane, 2-chloro,1,1-difluoroethane, 1-chloro-1,1,2,2-tetrafluoro ethane, 2-chloro, 1,1-difluoro ethane,

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chloroethane, chloropentafluoro ethane, dichlorotrifluoroethane, fluoro-ethane, hexafluoro-ethane, nitro-pentafluoro ethane, nitroso-pentafluoro ethane, perfluoro ethane, perfluoro ethylamine, ethyl vinyl ether, 1,1-dichloro ethylene, 1,1-dichloro-1,2-difluoro ethylene, 1,2-difluoro ethylene, Methane, Methane-sulfonyl chloride-trifluoro, Methane-sulfonyl fluoride-trifluoro, Methane-(pentafluorothio)trifluoro, Methane-bromo difluoro nitroso, Methane-bromo fluoro, Methane-bromo chloro-fluoro, Methane-bromo-trifluoro, Methane-chloro difluoro nitro, Methane-chloro dinitro, Methane-chloro fluoro, Methane-chloro trifluoro, Methane-chloro-difluoro, Methane-dibromo difluoro, Methane-dichloro difluoro, Methane-dichloro-fluoro, Methane-difluoro, Methane-difluoro-iodo, Methane-disilano, Methane-fluoro, Methane-iodo-trifluoro, Methane-nitro-trifluoro, Methane-nitroso-trifluoro, Methane-tetrafluoro, Methane-trichlorofluoro, Methane-trifluoro, Methanesulfenylchloride-trifluoro, 2- Methyl butane, Methyl ether, Methyl isopropyl ether, Methyl lactate, Methyl nitrite, Methyl sulfide, Methyl vinyl ether, Neon, Neopentane, Nitrogen, Nitrous oxide, 1,2,3-Nonadecane tricarboxylic acid-2-hydroxytrimethyleneester, 1-Nonene-3-yne, Oxygen, 1,4-Pentadiene, n-Pentane, Pentane-perfluoro, 2-Pantanone-4-amino-4-methyl, 1-Pentene, 2-Pentene {cis}, 2-Pentene {trans}, 1-Pentene-3-bromo, 1-Pentene-perfluoro, Phthalic acid-tetrachloro, Piperidine-2,3,6-trimethyl, Propane, Propane-1,1,1,2,2,3-hexafluoro, Propane-1,2-epoxy, Propane-2,2-difluoro, Propane-2-amino, Propane-2-chloro, Propane-heptafluoro-1-nitro, Propane-heptafluoro-1-nitroso, Propane-perfluoro, Propene, Propyl-1,1,1,2,3,3-hexafluoro-2,3 dichloro, Propylene-1-chloro, Propylene-chloro-{trans}, Propylene-2- chloro, Propylene-3-fluoro, Propylene-perfluoro, Propyne, Propyne-3,3,3-trifluoro, Styrene-3-fluoro, Sulfur hexafluoride, Sulfur (di)-decafluoro(S<sub>2</sub>F<sub>10</sub>), Toluene-2,4-diamino, Trifluoroacetonitrile, Trifluoromethyl peroxide, Trifluoromethyl sulfide, Tungsten hexafluoride, Vinyl acetylene, Vinyl ether, Xenon, 1-bromofluorobutane, and perfluoroethers.

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*B* 3. The therapeutic delivery system of claim 1 wherein said surfactant is selected from the group consisting of a lipid, a polymer, a protein, a polypeptide, a polysaccharide, a sugar, and an acrylate.

4. The therapeutic delivery system of claim 3 wherein said lipid is selected from the group consisting of fatty acids; lysolipids; phosphatidylcholine; dioleoylphosphatidylcholine; dimyristoylphosphatidylcholine; dipentadecanoylphosphatidyl-choline; dilauroylphosphatidylcholine; dioleoylphosphatidyl-choline; dipalmitoylphosphatidylcholine; distearoylphosphatidylcholine; phosphatidylethanolamine; dioleoylphosphatidylethanolamine; phosphatidylserine; phosphatidylglycerol; phosphatidylinositol; sphingolipids; sphingomyelin; glycolipids; ganglioside GM1; ganglioside GM2; glucolipids; sulfatides; glycosphingolipids; phosphatidic acid; palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers such as polyethyleneglycol, chitin, hyaluronic acid or polyvinylpyrrolidone; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides; cholesterol, cholesterol sulfate; cholesterol hemisuccinate; tocopherol hemisuccinate, lipids with ether and ester-linked fatty acids, polymerized lipids, diacetyl phosphate, stearylamine, cardiolipin, phospholipids with short chain fatty acids of 6-8 carbons in length, synthetic phospholipids with asymmetric acyl chains, 6-(5-cholest-3 $\beta$ -yloxy)-1-thio- $\beta$ -D-galactopyranoside, digalactosyldiglyceride, 6-(5-cholest-3 $\beta$ -yloxy)hexyl-6-amino-6-deoxy-1-thio- $\beta$ -D-galactopyranoside, 6-(5-cholest-3 $\beta$ -yloxy)hexyl-6-amino-6-deoxyl-1-thio- $\alpha$ -D-mannopyranoside, 12-(((7'-diethylaminocoumarin-3-yl)carbonyl)methylamino)-octadecanoic acid; N-[12-((7'-diethylaminocoumarin-3-yl)carbonyl)methyl-amino) octadecanoyl]-2-aminopalmitic acid; cholesteryl)4'-trimethyl-ammonio)butanoate; N-succinyldioleoylphosphatidylethanol-amine; 1,2-dioleoyl-sn-glycerol; 1,2-dipalmitoyl-sn-3-succinylglycerol; 1,3-dipalmitoyl-2-succinylglycerol; 1-hexadecyl-2-palmitoylglycerophosphoethanolamine; palmitoylhomocysteine; and/or combinations thereof; lauryltrimethylammonium bromide, cetyltrimethylammonium bromide, myristyltrimethylammonium bromide, alkylidimethylbenzylammonium chloride, benzylidemethyldodecylammonium bromide, benzylidemethylhexadecylammonium bromide, benzylidemethyltetradecylammonium bromide, cetyltrimethylammonium bromide, or cetylpyridinium bromide; pentafluoro octadecyl iodide, perfluorooctylbromide, perfluorodecalin, perfluorododecalin, perfluorooctyliodide,

perfluorotripropylamine, and perfluorotributylamine and further comprising a lipid bearing a covalently bound polymer.

5        5. A composition of claim 3 wherein said protein is selected from the group consisting of collagen, fibrin, and albumin.

6.        6. A composition of claim 3 wherein said polypeptide is selected from the group consisting of polyglutamic acid, polylysine, polyphosphazene, polyvinylalcohol, polyethyleneglycol, polypropyleneglycol, and a copolymer.

7.        7. A composition of claim 3 wherein said polysaccharide is selected from the group consisting of starch, HETA-starch, alginic acid, hyaluronic acid, cellulose, and a saccharide.

8.        8. A composition of claim 7 wherein said cellulose is methylcellulose.

15        9. A composition of claim 7 wherein said saccharide is dextran.

10.        10. A composition of claim 3 wherein said sugar is selected from the group consisting of glucose and galactose.

20        11. A composition of claim 3 wherein said polymer is selected from the group consisting of a synthetic polymer, a natural polymer, and a semisynthetic polymer.

12.        12. A composition of claim 11 wherein said synthetic polymer is polylactic acid.

13. A composition of claim 6 wherein said copolymer is selected from the group consisting of polylactideglycolide and polyethylene-polypropylene glycol.

5 14. A composition of claim 3 wherein said acrylate is methacrylate.

15. A composition of claim 14 wherein said methacrylate is methylmethacrylate.

10 16. A composition of claim 1 wherein said oil is selected from the group consisting of silicone oil, cod liver oil, mineral oil, plant oil, oil comprising fluorinated triglycerides, biocompatible saturated fatty acids, biocompatible unsaturated fatty acids, and biocompatible partially hydrogenated fatty acids, silicon-based oils, and synthetic oil.

15 17. A composition of claim 1 wherein said therapeutic is attached to the surface of said microsphere.

18. A composition of claim 1 wherein said therapeutic is encapsulated in said microsphere.

20 19. A composition of claim 1 wherein said microsphere is selected from the group consisting of a lyophilized microsphere, a spray-dried microsphere, a ball-milled microsphere, an agitated microsphere, and any combination thereof.

20. A composition of claim 16 wherein said plant oil is selected from the group consisting of peanut oil, canola oil, olive oil, safflower oil, corn oil, and mazola oil.

5            21. A composition of claim 16 wherein said silicon based oil is selected from the group consisting of vinyl-terminated, hydride terminated, silanol terminated, amino terminated, epoxy terminated, carbinol terminated fluids, mercapto-modified silicon fluid, saturated silicon oil, unsaturated, silicon oil, aryl-alkyl substituted silicon oil.

10            22. A composition of claim 16 wherein said synthetic oil is selected from the group consisting of saturated chains of C<sub>12</sub> to C<sub>24</sub> fatty acids and unsaturated chains of C<sub>12</sub> to C<sub>24</sub> fatty acids.

15            23. A composition of claim 22 wherein said synthetic oil is selected from the group consisting of glycerol triglyceride ester of oleic acid.

20            24. A targeted therapeutic delivery system of claim 1 further comprising a targeting ligand.

25            25. A method of preparing a targeted therapeutic delivery system comprising gas or gaseous precursor filled microspheres said method comprising the steps of processing a solution comprising an oil and a surfactant in the presence of a gaseous precursor, and adding to said microspheres a therapeutic compound, wherein said processing is selected from the group consisting of controlled agitation, controlled drying, and a combination thereof.

26. The method as in claim 25 wherein said method is carried out with a gaseous precursor at the activation temperature of the gaseous precursor.

27. The method as in claim 25 wherein the controlled agitation is selected from the group consisting of ball milling, shaking, vortexing, and a combination thereof.

28. The method as in claim 25 wherein the controlled drying is selected from the group consisting of lyophilizing, spray drying, and a combination thereof.

29. The method as in claim 25 further comprising the steps of filtering and heat sterilizing said aqueous lipid solution.

30. A method for the controlled delivery of a targeted therapeutic delivery system comprising:

(i) administering to a patient a targeted therapeutic delivery system comprising an oil, a surfactant, a gas or a gaseous precursor, and a therapeutic;

(ii) monitoring the targeted therapeutic delivery system using energy to determine the presence of the targeted therapeutic delivery system in the region; and

(iii) releasing the therapeutic from the targeted therapeutic delivery system in the region using energy.

31. A method of claim 30 for use in treating macular degeneration wherein said therapeutic comprises  $\alpha$ -tocopherol and retinoic acid, said oil is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, and 8 mol percent dipalmitoylphosphatidyl ethanolamine-polyethylene glycol 5000, and said gaseous precursor is perfluorobutane.

32. A method of claim 30 for use in treating retinoblastoma wherein said therapeutic comprises taxol and retinoic acid, said oil is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, and 8 mol percent dipalmitoylphosphatidyl ethanolamine-polyethylene glycol 5000, and said gaseous precursor is perfluorobutane.

5           33. A method of claim 30 wherein said therapeutic is amphotericin-B, said oil is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, 8 mol percent dipalmitoylphosphatidyl ethanolamine-polyethylene glycol 5000 and Pluronic F-68, and said gaseous precursor is perfluorobutane.

10           34. A method of claim 33 used to treat fungal ophthalmitis.

15           35. A method of claim 30 for treating retinitis pigmentosa wherein said therapeutic is bendazac, said oil is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, 8 mol percent dipalmitoylphosphatidyl ethanolamine-polyethylene glycol 5000 and Pluronic F-68, and said gaseous precursor is perfluorobutane.

20           36. A method of claim 30 for treating benign prostatic hyperplasia wherein said therapeutic is doxazosin, said oil is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, 8 mol percent dipalmitoylphosphatidyl ethanolamine-polyethylene glycol 5000 and Pluronic F-68, and said gaseous precursor is perfluorobutane.

25           37. A method of claim 30 wherein said therapeutic is  $\alpha$ -tocopherol, said surfactant comprises  $CF_3(CF_2)_8(CH_2)_6COOH$ , said oil is canola oil, and said gaseous precursor is perfluorobutane.

38. A method of claim 30 wherein said therapeutic is a dye, said oil is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidylcholine, 8 mol percent dipalmitoylphosphatidylethanolamine - polyethylene glycol 5000, and 10 mol percent dipalmitoylphosphatidic acid, said gaseous precursor is perfluoropropane.

39. A method of claim 30 wherein said therapeutic is dexamethasone, said surfactant comprises 82 mol percent dipalmitoylphosphatidylcholine, 8 mol percent dipalmitoylphosphatidylethanolamine - polyethylene glycol 5000, and 10 mol percent dipalmitoylphosphatidic acid, and said gas is perfluorobutane and nitrogen.

40. A method of claim 30 wherein said therapeutic is amphotericin, said surfactant comprises 82 mol percent dipalmitoylphosphatidylcholine, 8 mol percent dipalmitoylphosphatidylethanolamine - polyethylene glycol 5000, and 10 mol percent dipalmitoylphosphatidic acid, and said gas is selected from perfluorobutane and nitrogen.

41. A composition of claim 25 wherein said therapeutic comprises a dye.

42. A composition of claim 41 wherein said dye is selected from the group consisting of fluorescent dyes and colorimetric dyes.

43. A method of claim 30 for treating prostate cancer or benign prostate hypertrophy wherein said therapeutic is selected from the group consisting of testosterone, methyltestosterone, fluoxymesterone, finasteride, and 5a reductase enzyme inhibitors.

44. A method of claim 41 wherein said dye is selected from the group consisting of sudan black, fluorescein, R-Phycoerythrin, Texas red, BODIPY FL, oregon green, rhodamine red-X, tetramethylrhodamine, BODIPY TMR, BODIPY-TR, YOYO-1, DAPI, Indo-1, Cascade blue, fura-2, amino methylcoumarin, FM1-43, NBD, carbosy-SNARF, lucifer yellow, dansyl + R-NH<sub>2</sub>, propidium iodide, methylene blue, bromocresol blue, acridine orange, bromophenol blue, 7-amino-actinomycin D, allophycocyanin, 9-azidoacridine,

benzoxanthene-yellow, bisbenzidide H 33258 fluorochrome, 3HCl, 5-carboxyfluorescein diacetate, 4-chloro-1-naphthol, chromomycin-A<sub>3</sub>, DTAF, DTNB, ethidium bromide, fluorescein -5-maleimide diacetatae, mithramycin A, rhodamine 123, SBFI, SIST, tetramethylbenzidine, tetramethyl purpurate, thiazolyl blue, and TRITC.

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45. A method of claim 44 wherein said fluorescein is fluorescein isothiocyanate.

46. A method of claim 44 wherein said fluorescein isothiocyanate is selected from the group consisting of fluorescein isothiocyanate albumin, fluorescein isothiocyanate antibody conjugates, fluorescein isothiocyanate  $\alpha$ -bungarotoxin, fluorescein isothiocyanate-casein, fluorescein isothiocyanate-dextran, fluorescein isothiocyanate - insulin, fluorescein isothiocyanate - Lectins, fluorescein isothiocyanate - peroxidase, and fluorescein isothiocyanate - protein A.

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